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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER

NGUYEN, QUANG

ART UNIT	PAPER NUMBER
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1636

24

DATE MAILED: 07/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicati n No.

09/445,604

Applicant(s)

ABATANGELO ET AL.

Examiner

Quang Nguyen, Ph.D.

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-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 April 2003.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 162-194 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 162-194 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ | 6) <input type="checkbox"/> Other: |

DETAILED ACTION

Applicants' amendment filed on April 28, 2003 in Paper No. 23 has been entered.

New claims 162-194 are pending in the present application, and they are examined on the merits herein.

The text of those sections of Title 35 U.S.C. Code not included in this action can be found in a prior Office Action.

Specification

The abstract of the disclosure is objected to because it does not appear on a separate page (please note the 3 lines of text appearing prior to the heading ABSTRACT). Correction is required. See MPEP § 608.01(b).

Additionally, the abstract is objected because it contains the legal phraseology "said biologic material" on page 20, line 10. Correction is required.

Claim Objections

New claims 162, 183, 195 and 197-198 are objected to because of the following informalities: the terms "autocrosslinked" and "hylauroic" in A) and C), respectively, are misspelled. Appropriate correction is required.

New claim 166 is objected because there is a large empty space between the phrases " wherein the" and "skin adnexa" in the claim. Appropriate correction is required.

Respons to Applicants' Amendment

The 103 (a) rejections of record are withdrawn in light of Applicants' amendment.

Claim Rejections - 35 USC § 102

New claim 195 remains rejected under 35 U.S.C. 102(b) as being anticipated by Belline et al. (WO 96/37519) for the same reasons already set forth in the previous Office Action (page 5).

New claim 195 remains rejected under 35 U.S.C. 102(b) as being anticipated by Abatangelo et al. (WO 97/18842) as evidenced by della Valle et al. (U.S. Patent No. 4,851,521) or Dorigatti et al. (U.S. Patent No. 5,520,916) for the same reasons already set forth in the previous Office Action (pages 7-8).

Examiner would like to note that new claim 195 is essentially the same as claim 157, and that the cellular line is not required to be cultivated in the presence of a medium treated with fibroblasts or in a co-culture with fibroblasts.

Following is a new ground of rejection necessitated by Applicants' amendment.

Claim Rejections - 35 USC § 112

New claims 162-169, 173-182 and 196-199 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

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A biological material comprising: (a) at least one autologous or homologous cellular line selected from the group consisting of endothelial cells, glandular cells, skin adnexa and germinative cells of hair bulbs, (b) a biocompatible three-dimensional matrix, on which said cellular line is seeded and grown, said matrix comprising a hyaluronic acid derivative selected from the group recited in claim 162, 196, 197, 198, or 199, wherein said cellular line being cultivated in presence of a medium treated with autologous or homologous fibroblasts or in a co-culture with autologous or homologous fibroblasts;

does not reasonably provide enablement for the claimed biological materials containing any fibroblasts in a co-culture or in the presence of a medium treated with any fibroblasts. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

New claims 162-169 and 173-182 are drawn to a biological material comprising:
a) at least one autologous or homologous cellular line selected from the group consisting of endothelial cells, glandular cells, skin adnexa and germinative cells of hair

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bulbs; and b) a biocompatible three-dimensional matrix comprising at least one hyaluronic acid derivative selected from the recited group on which said cellular line is seeded and grown, and wherein said autologous or homologous cellular line is cultivated in presence of a medium treated with autologous or homologous fibroblasts or in a co-culture with fibroblasts. New claims 196-199 are also drawn to a similar biological material wherein the cellular line is cultivated in the presence of a medium treated with fibroblasts or in a co-culture with fibroblasts.

The specification teaches by exemplification the isolation and culture conditions in the presence of a three dimensional structure such as a non-woven HYAFF comprising a hyaluronic acid derivative for various cell types, including HUVEC, liver cell, islets of Langerhans and skin adnexa. The specification discloses that fragile cells such as endothelial cells, glandular cells and skin adnexa, germinative cells of hair bulbs and others can efficiently grow on a hyaluronic acid derivation matrix. Furthermore, the specification discloses optimal culture conditions for the growth of these cells in the hyaluronic acid derivative matrix, such as in the presence of a medium treated with fibroblasts or in a co-culture with fibroblasts seeded on the matrix at different time periods. The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for reasons discussed below.

(1) The breadth of the claims. As written, the claimed biological material encompasses both *in vivo* and *in vitro* biological materials having the recited characteristics. With respect to the *in vivo* biological materials of the present invention,

when read in light of the specification such biological materials are utilized in various applications such as in human and veterinary surgery, in skin and scalp transplants, in liver tissue transplants, to supplement insufficient insulin production *in vivo*, and as a support and use for gene transfection *in vivo*. The *in vivo* biological materials contain any fibroblasts (autologous, homologous or heterologous fibroblasts) or a medium derived thereof for the co-culture with at least one selected autologous or homologous cellular line in the biocompatible three-dimensional matrix.

(2) The state and unpredictability of the prior art. At the effective filing date of the present application, it is well recognized in the art that vigorous adverse host immune reactions would be elicited to reject the transplantation of xenogenic and allogeneic cells (Kohn, Clin. Exp. Immunol. 107:54-57, 1997; Cited previously). The adverse immunological reactions against non-autologous protein components as well as non-autologous cells in transplanted biological materials *in vivo* are also recognized by Abatangelo et al. (page 3, lines 7-10 and Summary of Invention; WO 97/18842; Cited previously). Additionally, the physiological art is recognized as unpredictable (MPEP 2164.03).

(3) The amount of direction or guidance provided. As enablement requires the specification to teach how to **make and use** the claimed invention, the instant specification fails to provide sufficient guidance or direction regarding to any *in vivo* use for the claimed biological materials containing any fibroblasts (autologous, homologous or heterologous fibroblasts) or a medium derived thereof for the co-culture with at least one selected autologous or homologous cellular line in the biocompatible three-

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dimensional matrix. It is unclear whether broadly claimed biological materials of the present invention could be maintained *in vivo* for any sufficient length of time in a host to carry out various *in vivo* functions contemplated by Applicants, particularly for the biological materials containing heterologous fibroblasts and/or a medium derived thereof, and in light of the state of the art discussed above. In the absence of sufficient teachings provided by the present application, it would have required undue experimentation for one skilled in the art to **use** the instant broadly claimed invention. Furthermore, as set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of sufficient guidance provided by the specification regarding to the issues noted above, the unpredictable nature the physiological arts in general, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to **use** the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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New claims 162-198 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 162, 183, 195, 197-198 and their dependent claims contain an improper Markush language by reciting "selected from the group consisting of: A); B).....; C).....; D)....". It is unclear whether the hyaluronic acid derivative is selected from each of the recited hyaluronic acid derivatives or various combinations of the hyaluronic acid derivatives and in which combinations? The metes and bounds of the claims are not clearly determined. As previously suggested, the term - - and - - should be inserted prior to D) in claims 162, 183, 197 or prior to C) in claims 195 and 198 to obviate this rejection.

Claim 170 recites the limitations "and biodegradable" and "optionally fibrin and/or collagen" in step ii) and "autologous or homologous human fibroblasts" in step iii). There is insufficient antecedent basis for these limitations in the claim. This is because the biological material of claim 162 does not recite the aforementioned limitations. A process for preparing the biological material of claim 162 should reflect the preparation of the same biological material.

In claim 171, the phrase "the same in step (iii) are optionally seeded in association with autologous or homologous keratinocytes" is unclear. This is because which is the same or not the same in step (iii)? Additionally, with the inclusion of autologous or homologous keratinocytes how can this step being the same with the step

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without the presence of autologous or homologous keratinocytes? The metes and bounds of the claims are not clearly determined.

Claim 172 recites the limitations "endothelial cells from human umbilical vein" in step i); "and biodegradable" and "optionally fibrin and/or collagen" in step iii); and "human autologous or homologous fibroblasts" in step iv). There is insufficient antecedent basis for these limitations in the claim. This is because the biological material of claim 162 does not recite the aforementioned limitations. A process for preparing the biological material of claim 162 should reflect the preparation of the same biological material. Additionally, it is unclear what is encompassed by the phrase "**optionally** in the presence of a medium treated with human autologous or homologous fibroblasts in primary culture or in a coculture with human autologous or homologous fibroblasts". It is noted that the biological material of claim 162 **requires** the autologous or homologous cellular line is cultivated in presence of a medium treated with autologous or homologous fibroblasts or in a coculture with fibroblasts, therefore this limitation should not be optional. The metes and bounds of the claim are not clearly determined.

In claim 181, the article "A" renders the claim indefinite. This is because only a single biological material having the recited characteristics is claimed in claim 162, and it is unclear which biological materials does claim 181 refer to?. To overcome this rejection, Examiner suggests the article - - The - - should be used instead of the article "A".

Claim 187 contains an improper Markush language by reciting "germinative cells are isolated from autologous, homologous, heterologous hair bulbs". It is not clear that

the germinative cells are isolated from hair bulbs in alternative forms. The term - - or - - should be inserted prior to the term "heterologous" to obviate this rejection.

Claim 191 recites the limitations "and biodegradable" and "optionally fibrin and/or collagen" in step ii) and "human fibroblasts" in step iii). There is insufficient antecedent basis for these limitations in the claim. This is because the *in vitro* biological material of claim 183 does not recite the aforementioned limitations. A process for preparing the *in vitro* biological material of claim 183 should reflect the preparation of the same biological material.

In claim 192, the phrase "in step (iii) the same is optionally seeded in association with keratinocytes" is unclear. This is because which is the same or not the same in step (iii)? And how can the step is the same with further seeding of keratinocytes? The metes and bounds of the claim are not clearly determined.

Claim 193 recites the limitations "endothelial cells from human umbilical vein" in step i); "and biodegradable" and "optionally fibrin and/or collagen" in step iii); and "human fibroblasts" in step iv). There is insufficient antecedent basis for these limitations in the claim. This is because the *in vitro* biological material of claim 183 does not recite the aforementioned limitations. A process for preparing the *in vitro* biological material of claim 193 should reflect the preparation of the same biological material. Additionally, as written it is unclear whether the presence of a medium treated with human fibroblasts in primary culture or in a coculture with human fibroblast in step iv) is also optional. The metes and bounds of the claim are not clearly determined.

Conclusion

No claims are allowed.


Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (703) 308-1906, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Quang Nguyen, Ph.D.


DAVID GUZO
PRIMARY EXAMINER